Chapter 7

PROGNOSTIC VALUE OF MINIMAL RESIDUAL DISEASE IN ESOPHAGEAL CANCER

Peter Scheuemann, Stefan B. Hosch, Jacob R. Izbicki

Department of General and Thoracic Surgery, Universitätsklinikum Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany

Abstract

A substantial proportion of patients (40% to 50%) with supposedly localized esophageal cancer who had undergone curative surgical treatment with complete tumour removal suffer from a metastatic tumour relapse within 24 months after surgery. A reason for such an early tumour relapse in these patients might be a minimal tumour cell dissemination (minimal residual disease, MRD) present at the time of operation, which cannot be detected by clinical and routine histopathological tumour staging procedures. Over the past 10 years, more sensitive immunohisto-/-cytochemical and nucleic acid based assays have been developed that are based on the detection of epithelial cell-or tumour-associated marker proteins and are able to detect single tumour cells or small tumour cell clusters present in lymph nodes classified as tumour-free by conventional histopathologic analysis, bone marrow or blood. Here we present an overview of recent studies concerning the prevalence and prognostic value of occult tumour cells in lymph nodes and bone marrow of patients with esophageal cancer identified by antibody or nucleic acid based assays.

INTRODUCTION

Despite advances in early diagnosis and more radical surgical treatment, prognosis of patients with esophageal carcinoma has not changed markedly over the last decades with reported postoperative survival rates of 10% to 36% (1–5). Approximately half of the patients develop early metastatic relapse after complete resection of their apparently localized primary tumours (6). It is therefore assumed that these patients had occult metastases already present at time of primary surgery and undetectable by current tumour staging methods. Over the past 10 years, more sensitive immunohisto-/-cytochemical and nucleic acid based methods have been developed that are based on the detection of epithelial cell-or tumour-associated markers and that are able to detect single tumour cells present in lymph nodes classified as tumour-free by conventional histopathologic analysis (7–14), bone marrow (6, 15–17) or blood (18–21) (see Table 1).

For the immunohisto-/-cytochemical detection of occult epithelial tumour cells in bone marrow and pathohistologically negative lymph nodes, most studies applied cytokeratins (CKs) as marker antigens. These proteins are stably,

K. Pantel (ed.), Micrometastasis, 127–138.

Table 1. Overview of immunhisto-/cytochemical assays used for detection of early disseminated tumour cells

Compartment of Tumour Cell Screening	Detection Antibodies (target proteins)	Detection Rate (%) [pos. LK (%)]	Prognostic Impact	Reference
LN	AE1/AE3 (CK)	20/78 (26) 40/574 (7)	No impact	34
LN	AE1/AE3 (CK)	14/37 (38)	DFS*, OS	38
LN	AE1/AE3 (CK)	15/41 (37)	OS	36
LN	Ber-EP4 (EpCAM)	*42/68 (62) total* *15/30 (50) pN0* [67/399 (17)]	DFS*, OS*	9
LN	Ber-EP4 (EpCAM)	89/126 (71)*total* 30/54 (56)*pN0* [150/634 (23)]	DFS*, OS* DFS*	8
LN	AE1/AE3 (CK)	39/59 (55.5)	OS	37
LN	AE1/AE3 (CK) anti-EMA (EMA)	26/115 (22.6)	Not evaluated	42
LN	AE1/AE3 (CK)	6/18 (33) *pNo* 15/46 (33) *total*	Not evaluated	41
BM	CK2 (CK)	1/8 (12.5)	Not evaluated	32
BM	CK2 (CK) A45-B/B3 (CK) KL1 (CK)	37/90 (41)	DFS, OS	6
BM	A45-B/B3 (CK)	25/68 (37)	No impact	9
BM	A45-B/B3 (CK)	28/79 (35)	DFS, OS	own data (not published)
BM	A45-B/B3 (CK)	29/75 (39)	OS*	31

Notes:

* Prognostic value was confirmed by multivariate analysis. Abbreviations: LN: lymph node; BM: bone marrow; CK: cytokeratin; EMA: epithelial-membrane antigen; DFS: disease-free survival; OS: overall survival.

abundantly and homogeneously expressed in a majority of epithelial tumours, including esophageal carcinoma (22). This extremely sensitive approach is able to detect 1 tumour cell in the background of 1×10^6 normal mononuclear bone marrow or lymph node cells (22). Performing this immunohisto-/-cytochemical approach, occult tumour cell detection rates of 12.5% to 41% for bone marrow and 26% to 56% for lymph nodes of esophageal cancer patients without overt lymph node metastatases (pN0) have been reported. For nucleic acid based tumour cell detection, most studies applied reverse transcriptase polymerase chain reaction (RT-PCR) assays to detect carcinoembryonic antigen (CEA) messenger RNA (mRNA), which is certainly expressed at different levels in a varity of gastrointestinal carcinoma, including esophageal carcinoma, with tumour cell detection rates between 5% and 55% in histopathologically negative lymph nodes.

Although an increasing number of published studies indicates that these early tumour cell deposits, especially in 'tumour-free' lymph nodes, appeared to be